REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112 are respectfully requested in light of the remarks which follow.

Claims 1-21, 23 and 24 are pending. Claims 2-6 and 23 are canceled by way of the present Amendment. Applicants reserve the right to file a divisional or continuation application directed to any subject matter canceled by way of this Amendment.

Claims 1, 7, 14 and 24 have been amended by way of the present Amendment, and new claims 25-32 added. Specifically, in the interest of expediting prosecution, the claims have been amended to recite the subject matter of claims 2-6 and 23, and to recite the treatment of a proliferative disease. Basis for these amendments and claims may be found throughout the specification and claims as filed, especially in claims 2-6 as filed, and on page 23, line 23 and page 24, lines 17-35, of the specification.

Priority

Applicants thank the Examiner for his acknowledgment of a claim for priority based on French Application No. 99 07181, filed on August 6, 1999. A certified copy of the French priority document will be forthcoming.

Claim Objections

Claims 23 and 24 are objected to because there are purportedly dash lines in front of claims 23 and 24. Claim 23 has been canceled by way of this amendment and claim 24

has been amended herein to remove the dash lines. Thus, Applicants respectfully submit that this objection is obviated.

Specification

The disclosure is objected to because the application purportedly does not contain an abstract. An Abstract of the Disclosure is attached herewith on a separate sheet. Applicants respectfully submit that the objection to the disclosure is obviated.

The description of the drawings for Figs. 2, 4, and 6 is objected to because of the phrase "the survival rate of these same mice". It is unclear to the Examiner which group of mice are the same mice to each figure. The specification has been amended herein to clarify that the expression "same mice" found in the description of Figures 2, 4 and 6, refers to the mice described in previous Figures 1, 3 and 5 respectively.

The description of the drawings for Fig. 6 is objected to because of the phrase "the following genes: huMIPα". The description for Fig. 6 has been amended herein to recite "the following genes: huMIP1α" as suggested by the Examiner. The description of the drawings for Fig. 6 is objected to because of the phrase "adenoviruses expressing the following genes: Tris buffer". It is unclear to the Examiner how an adenovirus can express Tris buffer. The specification has been amended to clarify that Figure 6 represents the survival rate of B6D2 mice implanted with p815 tumor cells. Groups of 15 mice are treated using compositions comprising adenoviruses expressing the following genes: huMIPlα + huIL2, huMIPlα + muIFNγ, huIL2 + muIFNγ or Tris buffer.

Figures 2, 3, 5, 6, and 7 are objected to because the contents in the inset are purportedly unclear. Substitute figures are attached herewith.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 1-5, 7, 11-15, 19, 20, 23, and 24 stand rejected under 35 U.S.C. § 112, first paragraph, as purportedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Office Action states that written description support exists for compositions comprising a nucleic acid sequence encoding MIP1α or MIP1β chemokine and natural variants of MIP1α or MIP1β. However, the Office Action asserts that there is no written description regarding which part of sequences of MIP1α or MIP1β or their natural variants or which part of IL-2 has the activity of the respective full length one or other MIPs.

In the interest of expediting prosecution, claim 1 has been amended herein to recite a composition for which the Office Actions states there is written description, *i.e.* a composition comprising a nucleic acid encoding MIP1α, MIP1β chemokine or natural variants of MIPα or MIP1β, and at least one nucleic acid encoding IL2.

Claims 1-5, 7,11-13,19, 20, 23 and 24 stand rejected under 35 U.S.C. §112, first paragraph, because the specification purportedly does not enable a person skilled in the art to make and use the invention commensurate in scope with these claims. The Office Action recognizes that the specification provides enablement for reducing tumor volume and increasing survival rate of a patient with solid tumors by intratumoral injection of a

composition comprising MIPlα or MIP1β and IL-2. However, the Office Action argues that the specification does not provide enablement for any other cytokine, any other administration route or any types of tumors. Applicants provide the following comments.

First, the Office Action asserts that the specification provides no evidence that injecting a MIP chemokine with a non IL-2 cytokine will result in a similar result as with IL-2, *i.e.* an increased survival rate and reduction of tumor volumes. Moreover, the Office Action argues that the specification does not provide any teaching regarding which "part" of MIP chemokine and IL-2 have the function of the respective full length one. The claims have been amended herein to recite a composition and a vector comprising a sequence encoding a full length IL-2 in combination with a sequence encoding MIPlα or MIP1β or natural variants thereof. These amendments obviate rejections regarding the use of a cytotoxic polypeptides other than IL-2 and of "part" of the encoded molecules.

Second, the Office Action argues that the specification does not provide any evidence that delivering of MIP1α or MIP1β in combination with IL-2 by a route of administration other than direct (intratumoral) injection will provide an antitumoral activity to the vaccinated host. The Office Action also argues that the specification only provides teaching for intratumoral injection with a dose of $5x10^8$ infectious units and that there is no teaching regarding the dose that should be used for different administration route. Applicants respectfully draw the Examiner's attention to page 24 lines 5-13 of the specification, which discloses the dose range of viral and plasmid vectors that can be used in the claimed compositions and formulations. The doses can be adjusted by the clinician as needed, *e.g.*, according to the type of tumors, the size and number of tumors, the weight

of the patients without undue experimentation and with a predictable degree of success. In fact, the methods of detecting expression or activity of lL-2 and MIP chemokines are standard techniques well known to those skilled in the art, as explained at least on pages 5 and 6 of the specification.

Finally, the Office Action asserts that with the exception of directly injecting the gene composition into implanted tumors, the specification fails to provide sufficient guidance to enable the skilled artisan to practice gene delivery to other type of tumors, such as leukemia, by systemic delivery. Applicants draw the Examiner's attention to the fact that the specification teaches a composition permitting the transfer and expression of MIPα or MIP1β gene in combination with IL-2. In fact, the specification discloses how to make (*see* Example 1) and to use (*see* Examples 2 and 3) the claimed invention. An antitumoral activity is demonstrated in three different tumor models, melanoma B16 cells, carcinoma RENCA cells and mastocytoma P815 cells respectively. The observations of the reduction of tumor volume and the increase of the survival rate in the three tumor models are directly correlated with a therapeutic effect. It is well recognized that an invention need not be exemplified in each of its embodiments. *Amgen, Incorporated v. Chugai Pharmaceutical Company, Limited*, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991). Thus, Applicants submit that the present application has provided sufficient disclosure with respect to the construction and use of the MIP1α+ IL-2 and MIP1β + IL-2 gene composition to enable the skilled artisan to practice the invention as broadly as it is now claimed.

Further, the amendments herein to claim 24 now recite the method of treatment to the direct administration into the tumor or at its periphery. Thus the claim is directed to the treatment of accessible tumors, *i.e.* solid tumors.

Claims 14 and 15 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a vector comprising a nucleic acid sequence encoding MIP chemokine and at least one nucleic acid sequence encoding a full length polypeptide having at least cytotoxic activity, purportedly does not reasonably provide enablement for a vector comprising a nucleic acid sequence encoding part of MIP chemokine and at least one nucleic acid sequence encoding part of a polypeptide having at least cytotoxic activity. The specification purportedly does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 14 has been amended herein to recite a vector for which the Office Action agrees there is written description, *i.e.* a vector comprising a nucleic acid encoding MIP chemokine and at least one nucleic acid encoding IL-2.

Thus, Applicants submit that the rejections under 35 U.S.C. § 112, first paragraph have been obviated.

Rejection under 35 U.S.C. §103

Claims 1-7, 11-15, 19, 20, 23, and 24 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Boursnell *et al.* (U.S. Patent No. 6,287,557) taken with

Hobart *et al.* (U.S. Patent No. 6,147,055) and Nakashima *et al.* (*Pharm Res* 13:1896-1901, (1996)).

The Office Action argues that Boursnell *et al.* disclose mutant virus vectors encoding nucleotide sequences expressing useful immunomodulating proteins including cytokines and chemokines, such as IL-2, MIP1α and MIP1β for cancer immunotherapy, where each of the heterologous nucleotide sequences can be placed under the control of any of a wide variety of known viral promoters or under the control of a known mammalian tissue-specific promoter.

Respectfully, Applicants traverse the rejection as follows. To make a *prima facie* case of obviousness, the Federal Circuit has articulated the analysis of a proper analysis under 35 U.S.C. § 103 as follows:

> [W]here claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *See, In re* Dow Chemical Co., . . . 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure.

In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). It respectfully is submitted that a legally sufficient *prima facie* case of obviousness has not been adduced, because the cited art, alone or in combination, do not teach or suggest the claimed vectors and compositions,

let alone that the claimed vectors and compositions could be used with a reasonable expectation of success.

Boursnell *et al.* disclose defective viral vectors containing a nucleic acid sequence encoding an immunomodulating polypeptide, such as cytokines or chemokines alone or in combination for conferring immunity against a pathogen or a tumor (*see* column 6 line 65-67, column 7 line 23-26 and column 8 lines 50-55). The working examples of Boursnell *et al.* disclose a mutant herpes virus encoding GM-CSF. Applicants note that IL-2 and MIP are listed together with more than 40 other immunomodulating polypeptides (*see* column 7 lines 1-14). With regard to two or more immunomoduiating polypeptides, Boursneil *et at.* disclose combinations involving IL-2, GM-CSF, lymphotactin and/or CD4OL (*see* column 8 lines 55-57). The combination of a MIP chemokine and IL-2 is neither disclosed nor suggested.

Hobart *et al.* disclose a composition comprising a plasmid DNA encoding IL-2 formulated with a cationic lipid mixture, for treating tumors. In a proposed trial, the IL-2 expressing composition is directly injected into solid tumor sites. Nakashima *et al.* disclose a composition comprising a plasmid DNA encoding MIP1α, for treating tumors. Reduced tumorigenicity and necrotic destruction of tumors were observed in animaLs implanted with transfected adenocarcinoma cells expressing either human or murine MIP1 α, whereas the transfer of iL-8 producing plasmid did not cause tumor growth inhibition and necrosis.

The Office Action argues that one of skill in the art of tumor gene therapy would be motivated to combine the teachings of Boursnell *et al.* with the teachings of Hobart *et al.*

and Nakashima *et al.* because both Hobart *et al.* and Nakashima *et al.* provide evidence of using nucleotide encoding IL-2 and hu-MIP1α, respectively, to achieve reducing tumor effects. Applicants respectfully submit that this is not the case.

The cited references do not suggest that one could use a combination of a MIP chemokine and LL-2. as recited in the present claims. Boursnell *et al.* provide a very general disclosure on anti-cancer therapies, using a herpes virus vector system to deliver immunomodulatoey genes in a solid tumor. Hobart *et al.* disclose using nucleic acid sequences encoding IL-2 to achieve antitumoral immunity. Nakashima *et al.* disclose using nucleic acid sequences encoding MIP1α to provide an effective antitumor effect.

Thus, the cited references contain no suggestion to combine the teachings of the references to arrive at the claimed invention. On the basis of Boursnell *et al.*, the skilled artisan would appreciate that a variety of immunomodulating polypeptides could be delivered via virus vectors in tumors, *i.e.* the 40 individual immunomodulatiflg polypeptides cited or combinations thereof. Boursnell *et al.* provide no guidance as to the choice of a combination of a MIP chemokine with IL-2 and provide no evidence that one skilled in the art would expect this specific combination to synergeticaily work and be effective for arititumor immunity. Hobart *et al.* do not remedy the deficiencies of Boursnell *et al.*, because this reference also fails to teach or suggest the direct administration of nucleic acid sequences encoding both a MIP chemokine and IL-2, to enhance the antitumorai effect provided by IL-2. Similarly, Nakashima *et al.* do not remedy the deficiencies of Boursnell *et al.*, because this reference likewise neither teaches

nor suggests to associate MIPlα gene transfer with a cytokine (*e.g.*, IL-2) to improve the antitumoral immunity provided by MIP1α.

Applicants note that the present specification recites data which demonstrate that vectors co-expressing MIP1α + IL-2 or MIP1β + IL-2 were found to be more effective for inhibiting tumor growth than vectors expressing individually a MIP or IL-2 molecule or other combinations. Therefore, the experimental data described in the present application have demonstrated an unexpected benefit of the claimed composition as compared to the disclosure of the cited references.

Moreover, it is well settled that before the teachings of two references can be combined, there must be some suggestion or motivation in the art to combine the teachings. References in combination do not make an invention obvious unless something in the prior references would suggest the advantage to be derived from combining their teachings. *In re Sernaker*, 217 USPQ 1, 6 (Fed. Cir. 1983). In this case, there is no suggestion whatsoever to combine the teachings of Hobart *et al.* and Nakashima *et al.* The technological teachings of the Hobart *et al.* are limited to the delivery of a IL-2 encoding plasmid. There is no suggestion in Hobart *et al.* to combine the IL-2 expressing plasmid with a gene which codes for a MIP chemokine. Nakashima *et al.*, on the other hand, proposes an approach to cancer therapy based on the transfer of the MIP1α gene. There is clearly no suggestion in Nakashima *et al.* to link the MIPlα gene to the IL-2 gene.

In conclusion, Applicants submit that none of the cited references teach or suggest to those of ordinary skill in the art that they should carry out the claimed compositions,

formulations and methods, and moreover, that a reasonable expectation of success has not been provided in the cited references, since they fail to establish that direct administration of vectors expressing both a MIP chemokine and IL-2 can synergetically works to successfully inhibit in vivo tumor growth.

Applicants respectfully request that the rejections be withdrawn.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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Date: April 16, 2003